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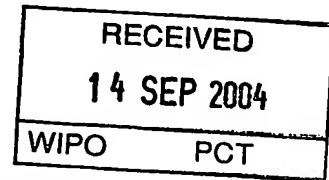


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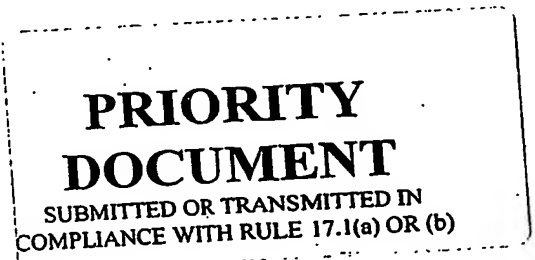
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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
If no title is shown please refer to the description.  
Si aucun titre n'est indiqué se referer à la description.)

METHOD FOR THE TREATMENT OF SCHIZOPHRENIA IN A PATIENT WITH OVERWEIGHT

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)  
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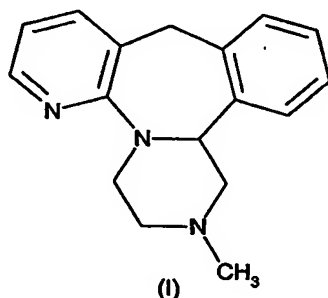
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PT RO SE SI SK TR LI

## A METHOD FOR THE PREPARATION OF ENANTIOMERICALLY PURE MIRTAZAPINE

The present invention relates to a method for the preparation of enantiomerically pure mirtazapine comprising ring closure with an acid.

5

Mirtazapine, 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine is a tetracyclic compound having the formula I:



The compound is chiral and the racemic mixture finds widespread use as a medicine for the treatment of depression. Other medical uses for mirtazapine have also been reported e.g., WO 99/25356 and WO 01/58453 disclose its use in the treatment of sleep disorders and apnea. Investigations into the biological effects of the enantiomers of mirtazapine (e.g. O'Connor and Leonard, *Neuropharmacology*, 1986, vol. 25, pp. 267-270; Kooyman et al., 1994, vol. 33, pp. 501-507; De Boer *et. al.*, *Neuropharmacology*, 1988, vol. 27, pp. 399-408; Gower et al., 1988, vol. 291, pp 185-201) invoke the use of the compound in its pure enantiomeric forms, which opens the need for efficient production of large quantities of enantiomerically pure mirtazapine. The present invention provides for improvement in such a production method.

A variety of methods are known in the art for the preparation of mirtazapine. US 4062848 describes variations within a four stage synthetic scheme by which the synthesis of mirtazapine can be accomplished starting from a 2-substituted nicotinitrile. Further modifications to various stages of this route have subsequently been described in WO 00/62782, WO 01/23345 and US 6,376,668.

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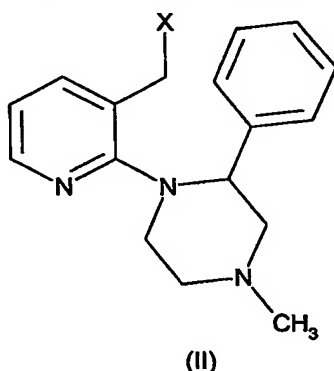
The preparation of enantiomerically pure mirtazapine has been addressed in US 4062848, WO 00/62782 and Selditz *et. al.*, 1998 (*J. Chromatography*, 1998, vol 803, pp 169-177). By the method disclosed in US 4062848, enantiomerically pure mirtazapine is obtained by fractional crystallisation of the diastereoisomeric salts formed by reaction of racemic mirtazapine with enantiomerically pure dibenzoyltartaric acid in ethanol followed

30

by regeneration of the free base by treatment with aqueous ammonia. Other methods of forming pure mirtazapine by recrystallisation of crude mirtazapine are disclosed in WO 00/62782. Selditz *et. al.* describe a chromatographic method to separate the enantiomers. In these methods resolution occurs at the end of the synthetic pathway

5 leading to the generation of a racemic mixture of mirtazapine. It follows therefore that the overall yield of each enantiomerically pure compound obtained is relatively low and can never be more than 50%. It would be beneficial to have a more economic method in which enantiomerically pure mirtazapine could be prepared with an overall improved yield.

10 According to the method described in US 4062848 mirtazapine can be obtained as a result of ring closure of a compound of formula (II),



wherein X represents a hydroxyl group, an esterified or etherified hydroxyl group or a halogen, using a variety of ring closing reagents. Examples of such reagents include

15 acids such as sulphuric acid, concentrated hydrochloric acid, picric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid (PPA), phosphorus oxychloride, phosphorus trioxide, phosphorus pentoxide and Lewis Acids such as aluminium chloride, ferric chloride, zinc chloride, tin chloride, titanium chloride, boron trifluoride, antimony pentachloride and zirconium tetrachloride. In US 4062848 preparation of mirtazapine is  
20 exemplified by ring closure using concentrated sulphuric acid. In WO 00/62782 it is indicated that concentrated sulphuric acid is most preferred.

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Surprisingly it has now been found that for the synthesis of enantiomerically pure mirtazapine by ring closure of an enantiomerically pure compound of formula (II),

25 stereochemical integrity in the starting material can be preserved by making a specific selection out of the above mentioned ring closing reagents.

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The present invention therefore provides a method comprising a step of ring closure of a compound of formula (II), wherein X is a leaving group, said step comprising treatment,

wherein mirtazapine with enantiomeric excess is formed by the ring closure of the compound of formula (II) with enantiomeric excess by treatment with a suitable acid in the absence of a solvent or a suitable combination of an acid and an organic solvent.

- 5 The term mirtazapine is used here in its generic meaning commonly used to refer to the chemical compound as a base and, depending on the context, to the salts and solvates thereof and supplemented with the prefixes (R) or (S) and/or (+) or (-) to the enantiomers of the compound. The (S) configuration causes positive optical rotation in the usual solvents.

10

The term enantiomeric excess in a compound refers to the difference between the amounts of each of the enantiomers present in a mixture, relative to the total amount of the compound in the mixture expressed as percentage. For example, in a 10 g mixture containing 9 g mirtazapine (90%), of which 4 g is (R)-mirtazapine and 5 g is (S)-

- 15 mirtazapine the (S)-mirtazapine is about 56% of total mirtazapine and the enantiomeric excess of the (S)-enantiomer is about 11%, which is the difference between, say, 55.556% and 44.444%. In an abbreviated manner the term mirtazapine or compound with enantiomeric excess refers to a mixture containing the mirtazapine or the compound with enantiomeric excess.

20

The invention can provide enantiomerically pure mirtazapine if enantiomerically pure starting material is used and the ring closure is effected by treatment with a suitable acid in the absence of a solvent or a suitable combination of an acid and an organic solvent.

- 25 Enantiomerically pure compound is one comprising less than 20 % of the other enantiomer, which is an enantiomeric excess of 60 %. Depending on the specific conditions of the invented method an enantiomerically pure compound having less than 10 % of the other enantiomer or less than 1 % of the other enantiomer can also be obtained. The yields of enantiomerically pure mirtazapine isolated are typically not less  
30 than 50 % but yields of not less than 70 % can also be obtained.

- A leaving group is a reactive function on a molecule which undergoes displacement from the molecule when a new bond is formed, as is commonly known in the art. More specifically a leaving group can be a hydroxyl group, an activated ester thereof, such as a  
35 carboxylate, a sulphonate or a phosphonate, or a halogen. Groups with this function are

commonly known in the art and the list can be further expanded by consultation of commonly available handbooks for organic synthesis.

A suitable acid for the method of the present invention is defined to be a specific acid or  
5 acid/solvent combination as mentioned hereafter or an acid or acid/solvent combination  
not mentioned hereafter, but which is obtained by performing a test as to the suitability of  
the acid. The test is to perform the ring closure with an acid, being a candidate acid, and  
starting material, which is compound II as defined above in a predetermined enantiomeric  
purity, and determine after the reaction the enantiomeric excess of the resulting  
10 mirtazapine. The quantitative degree of loss of enantiomeric purity can be determined by  
simple calculation and expressed as difference between enantiomeric excess in the  
starting material before the reaction and the enantiomeric excess of the product  
mirtazapine after the reaction. If the loss is less than 40% the acid or acid/solvent  
combination is a suitable acid or acid/solvent combination. A more strict criterion for a  
15 suitable acid or acid/solvent combination can be applied by selecting those causing a loss  
less than a number anywhere between 0% and 40%, such as 35%, 30%, 25%, 20%, 15%,  
10%, 5%, 2%, 1%, 0.5% and 0.3%. It is therefore an aspect of the invention to provide a  
method for the selection of an acid or acid/solvent combination suitable for the  
stereospecific ring closure leading to enantiomerically pure mirtazapine. The method  
20 comprises performing the ring closure reaction of an enantiomerically pure compound  
according to the formula II with the meaning of X, as defined previously with any  
candidate acid or any candidate acid/solvent combination and determining a loss of  
enantiomeric excess by the reaction and identifying an acid or an acid/solvent  
combination, as suitable if it results in the loss of less than 40%. Optionally, a stricter  
25 criterion, as mentioned above can be applied for more suitable acids or acid/solvent  
combinations.

A suitable acid used in the absence of solvent can be a protic acid or a protic acid  
derivative such as a protic acid anhydride. Concentrated sulphuric acid, the prior art  
30 method of choice for the preparation of racemic mirtazapine, or aluminium trichloride is  
not suitable.

For ring closure using a suitable acid in the absence of solvent, the use of polyphosphoric  
acid or phosphorus pentoxide in phosphoric acid are particularly preferred.

A suitable acid and organic solvent combination can be a combination of a protic acid or a protic acid derivative such as a protic acid anhydride or a mineral acid and a polar coordinating solvent such as ethanol or higher alcohols, DMF, DMA or *N*-methylpyrrolidinone.

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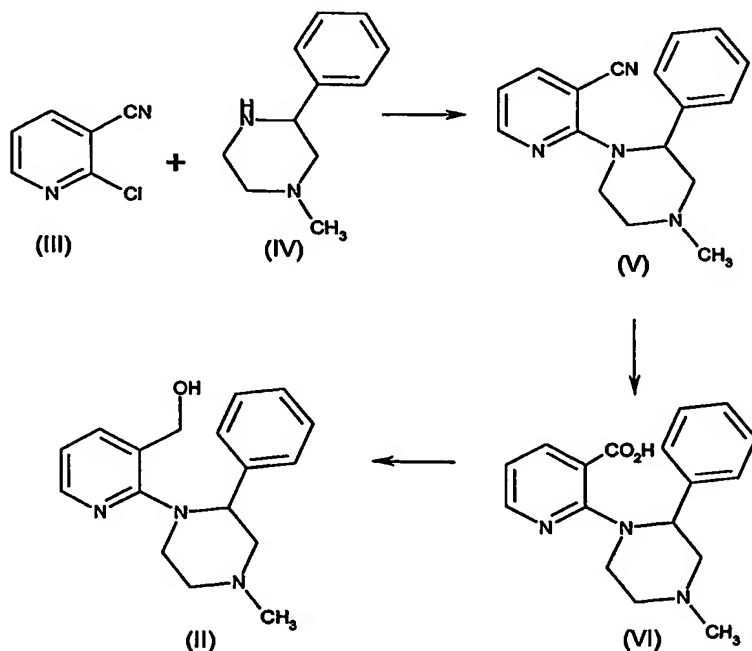
The acid/solvent combinations phosphorus pentoxide or polyphosphoric acid or sulfuric acid and xylene; phosphorus pentoxide or polyphosphoric acid and chlorobenzene; phosphorus pentoxide or polyphosphoric acid and toluene, and sulfuric acid and dichloromethane are not suitable.

10

More preferred is to use the combination of a protic acid derivative and *N*-methylpyrrolidinone or DMF. Polyphosphoric acid and *N*-methylpyrrolidinone or DMF are particularly preferred.

15 Whilst the ring closure reaction can take place at room temperature, the reaction can also be facilitated with additional heating. It is a further aspect of the invention therefore to include ring closure according to the methods of the present invention including additional heating.

20 A compound of formula (II) can be prepared by the synthetic route shown in Scheme I which is described in US 4062848.



Scheme 1

Thus, compound (V) can be prepared by reaction of compound (IV) with chloronicotinitrile (III) in an organic solvent, such as tetrahydrofuran or dimethylformamide, and in the presence of an equivalent of a base such as potassium fluoride. Compound (VI) can then  
 5 be prepared by hydrolysis of compound (V) using an aqueous base such as potassium hydroxide in an alcohol such as ethanol, typically at reflux. In WO 00/62782, it is described that the molar ratio of the base used to effect the nitrile hydrolysis can be reduced from 25 moles of base (as disclosed in the procedure of US patent 4062848) to around 12 moles of base. Finally compound (II) can be prepared by reduction of  
 10 compound (VI) again using a metal hydride such as lithium aluminium hydride in an organic solvent such as tetrahydrofuran. Conversion of the alcohol function to other leaving groups such as carboxylate and sulphonate esters and to halogens can be readily achieved by methods which are well known in the art.

15 Preparation of enantiomerically pure compound (II) can then be achieved by using methods well known in the art. For example, asymmetric synthesis methods e.g., synthesis with chiral induction, fractional crystallisation of diastereoisomeric salts formed upon reaction with a chiral acid or separation by chromatography on a chiral medium by normal or reverse phase chromatographic methods. Such methods are for example  
 20 described in 'Chirality in Industry' (edited by A.N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley)

In view of the newly found surprising utility it is a further aspect of the invention to provide the (+) or (-) enantiomers of the compound of formula (II) for use as optically pure starting  
 25 material for the ring closure reaction to obtain enantiomerically pure mirtazapine.

The invention also includes enantiomerically pure mirtazapine produced by the method of the present invention and pharmaceutical compositions of such for use in therapy. Such  
~~compositions can comprise a therapeutically effective amount of enantiomerically pure~~  
 30 mirtazapine in combination with pharmaceutically acceptable carriers and excipients which are well known in the art.

The invention is illustrated by the following examples:



**Example 1****Preparation of [S]-mirtazapine**

- 5 (S)-1-(3-Hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine (0.23 g, 1.03 mmol) was dissolved in *N*-methylpyrrolidinone (10 mL). The resulting solution was added dropwise to polyphosphoric acid (1.46 g) in *N*-methylpyrrolidone (5 mL) with stirring at 81 °C. The reaction mixture was stirred at 100°C for 72 h. It was then diluted with sodium hydroxide solution and diethyl ether. The organic layer was separated and washed twice with water.
- 10 Magnesium sulphate was added, removed by filtration and the filtrate was evaporated. The title compound (0.19 g, 68 %) was obtained as an oily product. The enantiomeric excess (e.e.) of the product was 99.2%.

**Example 2**

15

**Preparation of (S)-mirtazapine**

- (S)-1-(3-Hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine (0.30 g, 1.0587 mmole) was dissolved in 18.75 ml of dimethylformamide. To the solution 0.75 g dicalite and 1.5 g polyphosphoric acid was added. The reaction mixture was stirred for one day at 100 °C. It
- 20 was then diluted with sodium hydroxide and extracted with diethyl ether. The organic layer was washed twice with water, dried with magnesium sulphate, filtered and the filtrate was evaporated. The title compound (0.19 g, 68%) as obtained as an oily product. The e.e. of the product was 99.2%.

**Example 3****Preparation of (S)-mirtazapine**

- (S)-1-(3-Hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine (0.50 g, 1.76 mmole) was dissolved in *N*-methylpyrrolidone (7.5 ml) and heated to 100°C. To this mixture dicalite
- 30 (0.62 g) and phosphorus pentoxide (1.26 g) were added. After 66 hours the reaction was complete. Water was added to the reaction mixture. It was then filtered. The pH was adjusted to 14 by adding 4N sodium hydroxide solution. The aqueous solution was extracted with diethyl ether. The organic layer was dried with magnesium sulphate and evaporated. This provided the title compound (0.24 g, 51 %) with an e.e. of 99.7%.

35

**Example 4****Preparation of (S)-mirtazapine**

To [S]-1-(3-Hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine (0.5 g, 1.77 mmole)

- 5 was added polyphosphoric acid (9.6 g). The reaction mixture was heated to 100°C for 20 hours. The reaction mixture was diluted with water (6.5 ml) and the pH was brought to 8 by adding 4N sodium hydroxide solution. The water layer was extracted with ethyl acetate. The organic layer was washed with water, dried with magnesium sulphate and evaporated. This provided the title compound (0.29 g, 62%) with e.e. of 76%.

10

**Example 5****Preparation of (S)-mirtazapine**

To sulfuric acid (30.36 ml) at a temperature of 48 °C was added a solution of (S)-1-(3-

- 15 hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine (15.18 g, 51.05 mmole) in ethanol (30 ml). After 1 night an additional amount of sulfuric acid (30 ml) was added. After 4 hours the reaction was complete. Water (195 ml) was added followed by a sodium hydroxide solution (8.3 M) until a precipitate formed. The aqueous layer was extracted with ethyl acetate. The organic layer was subsequently washed with sodium hydroxide  
20 solution, then sodium chloride solution, dried with magnesium sulphate and evaporated. This yielded the title compound (7.97 g, 59%) with an e.e. of 62%.

**Example 6****25 Preparation of (S)-mirtazapine**

Concentrated sulphuric acid (2.2 ml) was added to (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine (0.29 g, 1.03 mmole). Dichloromethane was added to form a clear solution. The the dichloromethane was evaporated under reduced pressure at 40 °C.

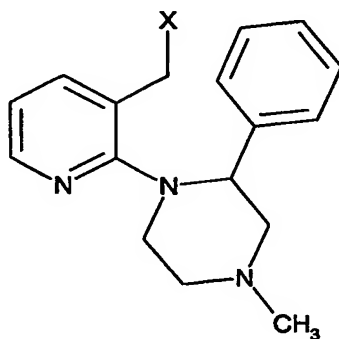
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The reaction mixture was stirred at 48 °C. After 4 hours the reaction was complete.

- 30 Sodium hydroxide solution (4 N) was added until an emulsion formed. The aqueous layer was extracted with diethyl ether. The diethyl ether was washed with water, dried with magnesium sulphate and evaporated. This gave the title compound (0.17 g, 62%) with an e.e. of 36%.
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## CLAIMS

1. A method for the preparation of enantiomerically pure mirtazapine, said method comprising a step of ring closure of a compound of formula (II)



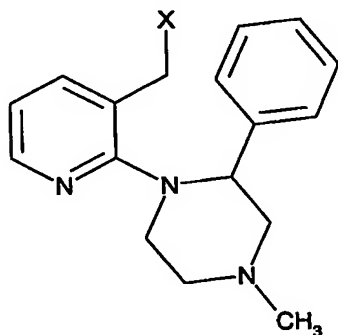
(II)

- 5 wherein X is a leaving group, said step comprising treatment with an acid, characterised in that mirtazapine with enantiomeric excess is formed by the ring closure of the compound of formula (II) with enantiomeric excess by treatment with a suitable acid in the absence of a solvent or a suitable combination of an acid and an organic solvent.
- 10 2. The method of claim 1, characterised in that the ring closure occurs using a suitable acid in the absence of a solvent.
- 15 3. The method of claim 2, characterised in that the acid is a protic acid or a protic acid derivative.
4. The method of claim 3, characterised in that the acid is polyphosphoric acid or phosphorus pentoxide in phosphoric acid.
- 20 5. The method of claim 1, characterised in that ring closure occurs using a suitable acid and organic solvent combination.
6. The method of claim 5, characterised in that the suitable acid and organic solvent combination is a protic acid or protic acid derivative in combination with a polar coordinating solvent.
- 25 7. The method of claim 5, characterised in that the suitable acid and organic solvent combination is a mineral acid in combination with a polar coordinating solvent.

8. The method of claim 6, characterised in that the suitable acid and organic solvent combination is polyphosphoric acid in combination with *N*-methylpyrrolidinone or DMF.
- 5 9. The method of any of claims 1-8 comprising additional heating.
10. A (+) or (-) enantiomer of the compound of formula (II) with X defined as in claim 1
11. A method for the selection of an acid or an acid/solvent combination suitable for a  
10 stereospecific ring closure reaction of an enantiomerically pure compound according to  
the formula II and meaning of X of claim 1 leading to enantiomerically pure mirtazapine  
comprising testing the reaction by treatment of the enantiomerically pure compound  
with a candidate acid or a candidate acid/solvent combination and determining a loss  
of enantiomeric excess by the reaction and identifying an acid or an acid/solvent  
15 combination, as suitable if it results in the loss of less than 40%.
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**Abstract**

The invention provides a method for the preparation of enantiomerically pure mirtazapine, said method comprising a step of ring closure of a compound of formula (II)



(II)

5

wherein X is a leaving group, said step comprising treatment with an acid, whereby mirtazapine with enantiomeric excess is formed by the ring closure of the compound of formula (II) with enantiomeric excess by treatment with a suitable acid in the absence of a solvent or a suitable combination of an acid and an organic solvent.

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